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1: J Virol. 1996 Jul;70(7):4623-31.

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Assemblons: nuclear structures defined by aggregation of immature capsids and some tegument proteins of herpes simplex virus 1.

Ward PL, Ogle WO, Roizman B.

The Marjorie B. Kovler Viral Oncology Laboratories, The University of Chicago, Illinois 60637, USA.

In cells infected with herpes simplex virus 1 (HSV-1), the viral proteins ICP5 (infected-cell protein 5) and VP19c (the product of UL38) are associated with mature capsids, whereas the same proteins, along with ICP35, are components of immature capsids. Here we report that ICP35, ICP5, and UL38 (VP19c) coalesce at late times postinfection and form antigenically dense structures located at the periphery of nuclei, close to but not abutting nuclear membranes. These structures were formed in cells infected with a virus carrying a temperature-sensitive mutation in the UL15 gene at nonpermissive temperatures. Since at these temperatures viral DNA is made but not packaged, these structures must contain the proteins for immature-capsid assembly and were therefore designated assemblons. These assemblons are located at the periphery of a diffuse structure composed of proteins involved in DNA synthesis. This structure overlaps only minimally with the assemblons. In contrast, tegument proteins were located in asymmetrically distributed structures also partially overlapping with assemblons but frequently located nearer to nuclear membranes. Of particular interest is the finding that the UL15 protein colocalized with the proteins associated with viral DNA synthesis rather than with assemblons, suggesting that the association with DNA may take place during its synthesis and precedes the involvement of this protein in packaging of the viral DNA into capsids. The formation of three different compartments consisting of proteins involved in viral DNA synthesis, the capsid proteins, and tegument proteins suggests that there exists a viral machinery which enables aggregation and coalescence of specific viral protein groups on the basis of their function.

1: Synapse. 1997 Nov;27(3):208-29.

Alzheimer disease hyperphosphorylated tau aggregates hydrophobically.

Ruben GC, Ciardelli TL, Grundke-Iqbal I, Iqbal K.

Department of Biological Sciences, Dartmouth College, Hanover, New Hampshire 03755, USA. George.C.Ruben@Dartmouth.Edu

The chemical interaction that condenses the hyperphosphorylated protein tau in Alzheimer's disease (AD P-tau) into neurofibrillary tangles and cripples synaptic transmission remains unknown. Only beta-sheet, positive ion salt bridges between phosphates, and hydrophobic association can create tangles of just AD P-tau. We have correlated transmission electron microscope (TEM) images of tau aggregation with different percentages of beta-sheet in aqueous suspensions of tau while using buffers that block dispositive or tripositive ionic bridges between intermolecular phosphates. Circular dichroism (CD) studies were performed at different temperatures from 5-85 degrees C using AD P-tau, AD P-tau dephosphorylated with hydrofluoric acid (HF AD P-tau) or alkaline phosphatase (AP AD P-tau), and recombinant human tau with 3-repeats and two amino terminal inserts (R-39) and using bovine tau (B tau) isolated without heat or acid treatment. Secondary structure was estimated from CD spectra at 5 degrees C using the Lincomb algorithm. Each preparation except one demonstrated an inverse temperature transition, Ti, in the CD at 197 nm. No correlation was found between beta-sheet content and aggregation, leaving only hydrophobic interaction as the remaining possibility. Thirteen of 21 possible phosphorylation sites in AD P-tau lie adjacent to positive residues in tau's primary structure. Occupation of five to nine phosphate sites on AD P-tau appears sufficient to reduce or neutralize tau's basic character. AD P-tau's hydrophobic character is indicated by its low inverse temperature transition, Ti. The Ti for AD P-tau was 24.5 degrees C or 28 degrees C, whereas for B tau with three phosphates it was 32 degrees C, for unphosphorylated tau R-39 it was 38 degrees C, and for dephosphorylated HF AD P-tau it was 37.5 degrees C. The hydrophobic protein elastin and its analogs coalesce and precipitate at their Ti of 24-29 degrees C, well below body temperature. We

hypothesize that AD P-tau causes tangle accumulation by this mechanism.

PMID: 9329157 [PubMed - indexed for MEDLINE]

1: Science. 1998 Jul 10;281(5374):253-6. Related Articles, Links

Design of a 20-amino acid, three-stranded beta-sheet protein.

Kortemme T, Ramirez-Alvarado M, Serrano L.

European Molecular Biology Laboratory (EMBL), Meyerhofstrasse 1, Heidelberg D-69117, Germany.

A 20-residue protein (named Betanova) forming a monomeric, three-stranded, antiparallel beta sheet was designed using a structural backbone template and an iterative hierarchical approach. Structural and physicochemical characterization show that the beta-sheet conformation is stabilized by specific tertiary interactions and that the protein exhibits a cooperative two-state folding-unfolding transition, which is a hallmark of natural proteins. The Betanova molecule constitutes a tractable model system to aid in the understanding of beta-sheet formation, including beta-sheet aggregation and amyloid fibril formation.

PMID: 9657719 [PubMed - indexed for MEDLINE]

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1: Biochemistry. 1998 Jul 14;37(28):10223-30. Related Articles, Links

Rapid assembly of Alzheimer-like paired helical filaments from microtubule-associated protein tau monitored by fluorescence in solution.

Friedhoff P, Schneider A, Mandelkow EM, Mandelkow E.

Max-Planck-Unit for Structural Molecular Biology, Hamburg, Germany.

Alzheimer's disease is characterized by the progressive deposition of two types of fibers in the affected brains, the amyloid fibers (consisting of the Abeta peptide, generating the amyloid plaques) and paired helical filaments (PHFs, made up of tau protein, forming the neurofibrillary tangles). While the principles of amyloid aggregation are known in some detail, the investigation of PHF assembly has been hampered by the low efficiency of tau aggregation, the requirement of high protein concentrations, and the lack of suitable detection methods. Here we report a quantitative assay system that permits monitoring of the assembly of PHFs in real time by the fluorescence of dyes such as thioflavine S or T. Using this assay, we evaluated parameters that influence the efficiency of filament formation. Disulfide-linked dimers of tau constructs representing the repeat domain assemble into PHFs most efficiently, but other tau isoforms or constructs form bona fide PHFs as well. The rate of assembly is greatly enhanced by polyanions such as RNA, heparin, and notably polyglutamate which resembles the acidic tail of tubulin. The assembly is optimal at pH approximately 6 and low ionic strengths (<50 mM) and increases steeply with temperatures above 30 degreesC, indicating that it is an entropy-driven process.

PMID: 9665729 [PubMed - indexed for MEDLINE]

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1: Biotechnology (N Y). 1995 Sep;13(9):988-93. Related Articles, Links

Erratum in:
- Biotechnology 1995 Nov;13(11):1142.

A biotechnological method provides access to aggregation competent monomeric Alzheimer's 1-42 residue amyloid peptide.

Dobeli H, Draeger N, Huber G, Jakob P, Schmidt D, Seilheimer B, Stuber D, Wipf B, Zulauf M.

Pharma Division, F. Hoffmann-La Roche, Basel, Switzerland.
heinz.doebeli@roche.com

Senile plaques, a neuropathological hallmark of Alzheimer's disease, consist primarily of insoluble aggregates of beta-amyloid peptide (A beta). A 42-residue peptide (A beta 1-42) appears to be the predominant form. In contrast to A beta 1-40, A beta 1-42 is characterized by its extreme tendency to aggregate into fibers or precipitate. A tailored biotechnological method prevents aggregation of A beta 1-42 monomers during its production. The method is based on a protein tail fused to the amino terminus of A beta. This tail leads to a high expression in E. coli, and a histidine affinity tag facilitates purification. Selective cleavage of the fusion tail is performed with cyanogen bromide by immobilizing the fusion protein on a reversed phase chromatography column. Cleavage then occurs only at the methionine positioned at the designed site but not at the methionine contained in the membrane anchor sequence of A beta. Furthermore, immobilization prevents aggregation of cleaved A beta. Elution from the HPLC column and all succeeding purification steps are optimized to preserve A beta 1-42 as a monomer. Solutions of monomeric A beta 1-42 spontaneously aggregate into fibers within hours. This permits the investigation of the transition of monomers into fibers and the correlation of physico-chemical properties with biological activities. Mutations of A beta 1-42 at position 35 influence the aggregation properties. Wild-type A beta 1-42 with methionine at position 35 has similar properties as A beta with a methionine sulfoxide residue. The fiber formation tendency, however, is reduced when position 35 is occupied by a glutamine, serine, leucine, or a glutamic acid residue.

1: J Neuropathol Exp Neurol. 1998 Jan;57(1):76-94.

N-terminal heterogeneity of parenchymal and cerebrovascular Abeta deposits.

Tekirian TL, Saido TC, Markesbery WR, Russell MJ, Wekstein DR, Patel E, Geddes JW.

Sanders-Brown Center on Aging, Department of Anatomy and Neurobiology, University of Kentucky, Lexington 40536-0230, USA.

The goals of this study were twofold: to determine whether species differences in Abeta N-terminal heterogeneity explain the absence of neuritic plaques in the aged dog and aged bear in contrast to the human; and to compare Abeta N-terminal isoforms in parenchymal vs cerebrovascular Abeta (CVA) deposits in each of the species, and in individuals with Alzheimer disease (AD) vs nondemented individuals. N-terminal heterogeneity can affect the aggregation, toxicity, and stability of Abeta. The human, polar bear, and dog brain share an identical Abeta amino acid sequence. Tissues were immunostained using affinity-purified polyclonal antibodies specific for the L-aspartate residue of Abeta at position one (AbetaN1[D]), D-aspartate at N1 (AbetaN1[rD]), and pyroglutamate at N3 (AbetaN3[pE]) and p3, a peptide beginning with leucine at N17 (AbetaN17 [L]). The results demonstrate that each Abeta N-terminal isoform can be present in diffuse plaques and CVA deposits in AD brain, nondemented human, and the examined aged animal models. Though each Abeta N-terminal isoform was present in diffuse plaques, the average amyloid burden of each isoform was highest in AD vs polar bear and dog (beagle) brain. Moreover, the ratio of AbetaN3(pE) (an isoform that is resistant to degradation by most aminopeptidases) vs AbetaN17(L)-x (the potentially nonamyloidogenic p3 fragment) was greatest in the human brain when compared with aged dog or polar bear. Neuritic plaques in AD brain typically immunostained with antibodies against AbetaN1(D) and AbetaN3 (pE), but not AbetaN17(L) or AbetaN1(rD). Neuritic deposits in nondemented individuals with atherosclerotic and vascular hypertensive changes could be identified with AbetaN1(D), AbetaN3(pE), and AbetaN1 (rD). The presence of AbetaN1(rD) in neuritic plaques in nondemented individuals with atherosclerosis or hypertension, but not in AD, suggests a

different evolution of the plaques in the two conditions. AbetaN1(rD) was usually absent in human CVA, except in AD cases with atherosclerotic and vascular hypertensive changes. Together, the results demonstrate that diffuse plaques, neuritic plaques, and CVA deposits are each associated with distinct profiles of Abeta N-terminal isoforms.

PMID: 9600199 [PubMed - indexed for MEDLINE]

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1: Blood. 1987 Apr;69(4):1073-81. Related Articles, Links

Studies on the ultrastructure of fibrin lacking fibrinopeptide B (beta-fibrin).

Mosesson MW, DiOrio JP, Muller MF, Shainoff JR, Siebenlist KR, Amrani DL, Homandberg GA, Soria J, Soria C, Samama M.

Release of fibrinopeptide B from fibrinogen by copperhead venom procoagulant enzyme results in a form of fibrin (beta-fibrin) with weaker self-aggregation characteristics than the normal product (alpha beta-fibrin) produced by release of fibrinopeptides A (FPA) and B (FPB) by thrombin. We investigated the ultrastructure of these two types of fibrin as well as that of beta-fibrin prepared from fibrinogen Metz (A alpha 16 Arg----Cys), a homozygous dysfibrinogenemic mutant that does not release FPA. At 14 degrees C and physiologic solvent conditions (0.15 mol/L of NaCl, 0.015 mol/L of Tris buffer pH 7.4), the turbidity (350 nm) of rapidly polymerizing alpha beta-fibrin (thrombin 1 to 2 U/mL) plateaued in less than 6 min and formed a "coarse" matrix consisting of anastomosing fiber bundles (mean diameter 92 nm). More slowly polymerizing alpha beta-fibrin (thrombin 0.01 and 0.001 U/mL) surpassed this turbidity after greater than or equal to 60 minutes and concomitantly developed a network of thicker fiber bundles (mean diameters 118 and 186 nm, respectively). Such matrices also contained networks of highly branched, twisting, "fine" fibrils (fiber diameters 7 to 30 nm) that are usually characteristic of matrices formed at high ionic strength and pH. Slowly polymerizing beta-fibrin, like slowly polymerizing alpha beta-fibrin, displayed considerable quantities of fine matrix in addition to an underlying thick cable network (mean fiber diameter 135 nm), whereas rapidly polymerizing beta-fibrin monomer was comprised almost exclusively of wide, poorly anastomosed, striated cables (mean diameter 212 nm). Metz beta-fibrin clots were more fragile than those of normal beta-fibrin and were comprised almost entirely of a fine network. Metz fibrin could be induced, however, to form thick fiber bundles (mean diameter 76 nm) in the presence of albumin at a concentration (500 mumol/L) in the physiologic range and resembled a Metz plasma fibrin clot in that regard. The diminished capacity of Metz beta-fibrin to form thick fiber bundles may be due to impaired use or occupancy of a polymerization site exposed by FPB release. Our results indicate that twisting fibrils are an

inherent structural feature of all forms of assembling fibrin, and suggest that mature beta-fibrin or alpha beta-fibrin clots develop from networks of thin fibrils that have the ability to coalesce to form thicker fiber bundles.

PMID: 3548843 [PubMed - indexed for MEDLINE]

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1: AIDS Res Hum Retroviruses. 1993 Jul;9(7):677-85. Related Articles, Links

HIV-1 Tat alters normal organization of neurons and astrocytes in primary rodent brain cell cultures: RGD sequence dependence.

Kolson DL, Buchhalter J, Collman R, Hellmig B, Farrell CF, Debouck C, Gonzalez-Scarano F.

Department of Neurology, University of Pennsylvania Medical Center, Philadelphia 19104.

The HIV-1 trans-activator protein Tat has been implicated as a mediator of neuronal dysfunction in several model systems. To explore the possibility that Tat can affect primary brain cells, we examined the effect of recombinant Tat protein on rat cortical brain cell cultures. Tat induced marked aggregation of neurons and astrocytes in developing cultures and caused the neuritic processes to coalesce into fascicles. Cell death was not seen and brain macrophages were not affected. These effects mapped to a different region from the trans-activation domain of Tat, as mutating the RGD (arginine-glycine-aspartic acid) sequence within the second exon abrogated aggregation and fascicle formation without affecting trans-activation capacity. Such effects on primary neurons and astrocytes may reflect specific interactions of Tat with uninfected cells within the CNS in vivo.

PMID: 8369172 [PubMed - indexed for MEDLINE]

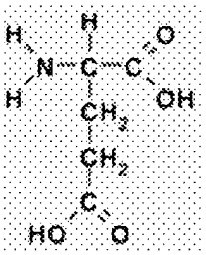
Glutamic acid

From Wikipedia, the free encyclopedia.
(Redirected from Glutamate)

Glutamic acid or **glutamate** is one of the 20 most common natural amino acids. As its name indicates, it is acidic, with a carboxylic acid component to its side chain.

Its three-letter abbreviation is **Glu**, and its one-letter abbreviation is **E**. A three-letter designation for either glutamine or glutamic acid is **Glx** (one-letter abbreviation: **Z**).

Glutamic acid is critical for proper cell function, but it is not considered an essential nutrient in humans because the body can manufacture it from simpler compounds.

Glutamic acid	
Chemical name	Glutamic acid
Chemical formula	$C_5H_9NO_4$
Molecular mass	147.13 g mol^{-1}
Melting point	247-249 °C
Boiling point	xx.x °C
Density	x.xxx g cm^{-3}
CAS number	56-86-0
SMILES	xxx
	
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Contents

Neurotransmitter

In addition to being one of the building blocks in protein synthesis, it is the most widespread neurotransmitter in brain function, as an excitatory neurotransmitter and as a precursor for the synthesis of GABA in GABAergic neurons. Glutamate activates both ionotropic and metabotropic glutamate receptors. The ionotropic ones being non-NMDA (AMPA and kainate) and NMDA receptors. Free glutamic acid cannot cross the blood-brain barrier in appreciable quantities; instead it is converted into L-glutamine, which the brain uses for fuel and protein synthesis.

It is conjectured that glutamate is involved in cognitive functions like learning and memory in the brain, though excessive amounts may cause neuronal damage associated in diseases like amyotrophic lateral sclerosis, lathyrism, and Alzheimer's disease. Also, the drug phencyclidine (more commonly known as PCP) antagonizes glutamate at the NMDA receptor, causing behavior reminiscent of schizophrenia.

Glutamate in action is extremely difficult to study due to its transient nature. A team at Stanford University has developed a nanosensor to detect the release of glutamate by nerve cells.

The sensor, constructed of proteins, has a pair of lobes that are hinged like a Venus flytrap. When glutamate binds to the proteins, the lobes snap shut. Two flourescent jellyfish proteins are attached to the sensor. One of these proteins emits both blue light and excites a second protein that emits yellow light. When the lobes snap shut on glutamate, the blue protein moves away from the yellow protein, decreasing the glow from the yellow. A dimming of the yellow light indicates that glutamate has been released from a nerve cell. The sensor can currently only be located on the surface of cell so it can only indicate glutamate activity outside the cell. (Okumoto, *et al.*, 2005)

Neurotoxicity

In excess, glutamate causes neuronal damage and eventual cell death, particularly when NMDA receptors are activated. This may be due to:

- High intracellular Ca[sup]2+[/sup] exceeding storage capacity and damaging mitochondria, leading to release of cytochrome p450 and apoptosis.
- Glutamate/calcium-mediated promotion of transcription factors for pro-apoptotic genes, or downregulation of transcription factors for anti-apoptotic genes.

These theories are based on the observation that epileptic patients often show evidence of neurodegeneration on post-mortem examination.

Seizures

Glutamate has been implicated in epileptic seizures. Microinjection of glutamate into neurons produces spontaneous depolarisations around one second apart, and this firing pattern is similar to what is known as paroxysmal depolarising shift in epileptic attacks. It's been suggested that a fall in resting membrane potential at seizure foci could cause spontaneous opening of VOCCs, leading to glutamate release and further depolarisation.

Food

The sodium salt of glutamic acid, monosodium glutamate (MSG) is responsible for one of the five basic tastes of the human sense of taste (umami), and MSG is extensively used as a food additive.

References

- Okumoto, S., *et al.* (2005). "Detection of glutamate release from neurons by genetically encoded surface-displayed FRET nanosensors". *Proceedings of the National Academy of Sciences* **In Press** (): .

Amino acids

Alanine | Arginine | Asparagine | Aspartic acid | Cysteine | **Glutamic acid** | Glutamine | Glycine | Histidine | Isoleucine | Leucine | Lysine | Methionine | Phenylalanine | Proline | Serine | Threonine | Tryptophan | Tyrosine | Valine

Essential amino acid | Protein | Peptide | Genetic code

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